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EDITORIAL

Using diuretic therapy in the critically ill patient

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Diuretics are routinely prescribed in critically ill patients but significant variation in practise exists. In this article, we summarise current data relevant to diuretic prescribing.

What are the indications for diuretics in critically ill patients?

Diuretics are first-line therapy to remove excess fluid, as monotherapy or in combination using loop diuretics, carbonic anhydrase inhibitors, thiazides, and thiazide-like drug classes. Mineralocorticoid receptor antagonists (MRAs) are used less frequently but may be prescribed to offset adverse effects of other diuretics (e.g. for hypokalemia due to loop diuretics).

Common indications for diuretics in critically ill patients include: (i) conditions where fluid accumulation negatively impacts organ function; (ii) situations where continued fluid administration is necessary despite risk of fluid accumulation and (iii) adjunctive management of hypertension. Less common indications are (i) osmotherapy to manage elevated intracerebral pressure and (ii) need for forced diuresis to eliminate toxic substances or manage tumour lysis syndrome. Oliguria alone is not an indication [1].

The goal is to increase urine output and decrease intravascular hydrostatic pressure, interstitial oedema and compartmental pressures. Surrogate measures for raised intravascular hydrostatic pressure include elevated central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), natriuretic peptides and signs of oedema on imaging [2]. When available, extravascular lung water as determined by transpulmonary thermodilution also correlates with pulmonary oedema.

How to monitor diuretic therapy

Monitoring diuretic therapy involves assessment of the balance between effectiveness (i.e. diuresis, resolution of fluid accumulation) and safety. Indicators of effective fluid removal and decongestion include clinical signs (e.g. improved respiratory status), decreasing levels of natriuretic peptides, improved organ function [i.e. improved serum creatinine (SCr), improved oxygenation], resolution of congestion on imaging and decrease in CVP or PCWP. Doppler-based scores have gained interest in evaluating organ venous congestion under the acronym VexuS. Whilst this approach is satisfactory, it is not always feasible to acquire satisfactory Doppler signals and requires training.

What if patients are diuretic responsive but urine output is too low or the prescribed fluid balance cannot be achieved?

Diuretic efficacy decreases in the setting of hypovolemia, refractory venous congestion, inadequate concentrations at sites of action (i.e. haemodynamic instability, inadequate dose) and insufficient renal function. Patients with impaired kidney function, i.e. with acute kidney injury (AKI) or chronic kidney disease (CKD), may require higher doses of diuretics. Inadequate or declining urine output may suggest that the dose may be too low or that intravascular hypovolemia has developed. Both should lead to re-evaluation of diuretic indication and dose.

Venous congestion (e.g. cardiorenal syndrome) may also reduce the response to diuretics and should trigger escalation (i.e. higher dose, change of administration route or combination therapy). In patients with acute decompensated heart failure, sodium–glucose co-transporter-2 (SGLT2) inhibitors increase the daily

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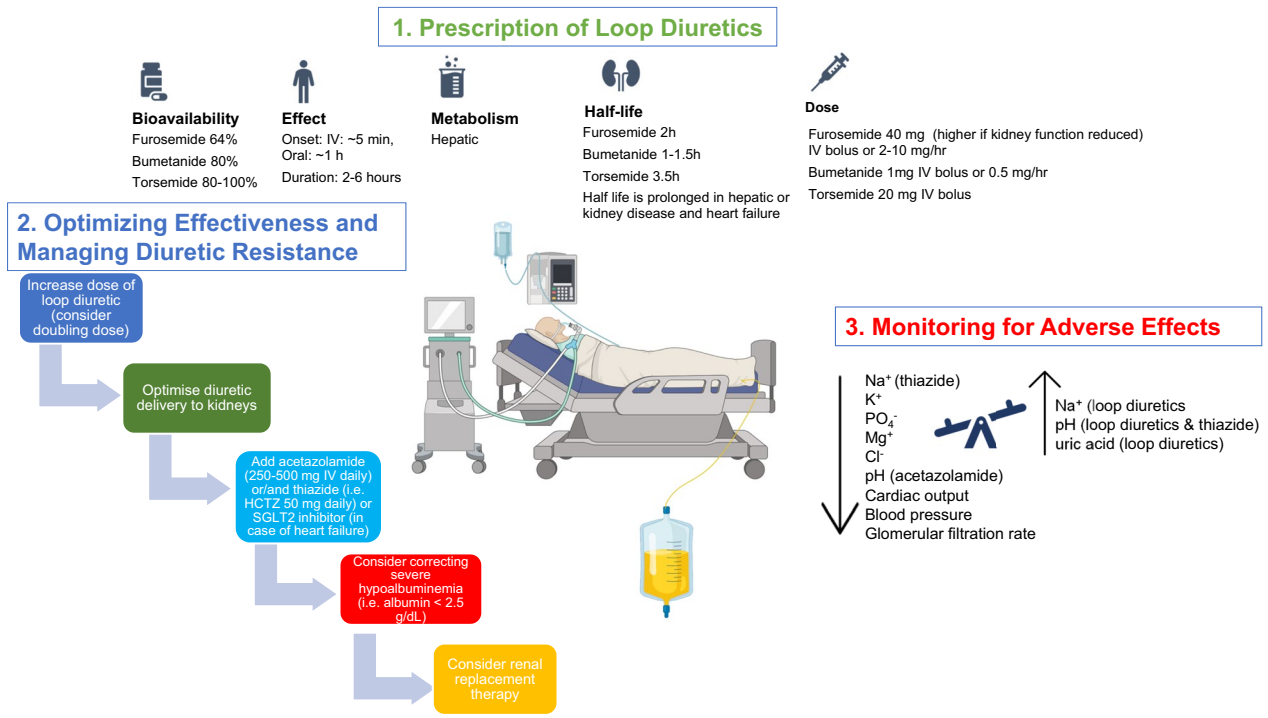
1. Prescription of Loop Diuretics
Bioavailability
Furosemide 64%
Bumetanide 80%
Torsemide 80-100%
Effect
Onset: IV: ~5 min, Oral: ~1 h
Duration: 2-6 hours
Metabolism
Hepatic
Half-life
Furosemide 2h
Bumetanide 1-1.5h
Torsemide 3.5h
Half life is prolonged in hepatic or kidney disease and heart failure
Dose
Furosemide 40 mg (higher if kidney function reduced) IV bolus or 2-10 mg/hr
Bumetanide 1mg IV bolus or 0.5 mg/hr
Torsemide 20 mg IV bolus
2. Optimizing Effectiveness and Managing Diuretic Resistance
Increase dose of loop diuretic (consider doubling dose)
Optimise diuretic delivery to kidneys
Add acetazolamide (250-500 mg IV daily) or/and thiazide (i.e. HCTZ 50 mg daily) or SGLT2 inhibitor (in case of heart failure)
Consider correcting severe hypoalbuminemia (i.e. albumin < 2.5 g/dL)
Consider renal replacement therapy
3. Monitoring for Adverse Effects
Na+ (thiazide)
K+
PO4-
Mg+
Cl-
pH (acetazolamide)
Cardiac output
Blood pressure
Glomerular filtration rate
Na+ (loop diuretics
pH (loop diuretics & thiazide)
uric acid (loop diuretics)

Fig. 1 Diuretic prescribing and monitoring. The figure depicts factors to consider when selecting a loop diuretic, monitoring effectiveness and safety, and managing potential diuretic resistance. *HCTZ* hydrochlorothiazide; *IV* intravenous; *SGLT2* sodium-glucose co-transporter-2

urinary output and should be considered in combination with other diuretics in this setting [3]. Accurate evaluation of fluid status is necessary to guide decision-making and differentiate between intravascular hypovolemia and venous congestion [4]. Signs of volume depletion on ultrasound include collapsible inferior vena cava and hyperkinetic movements (i.e. kissing heart on cardiac ultrasound). Indicators of fluid responsiveness, low CVP or hemoconcentration (i.e. rising plasma protein concentration) should prompt cessation of diuretics in patients with signs of hypoperfusion (e.g. rising plasma lactate, cold extremities, mottled skin, prolonged capillary refill time). If fluid accumulation and congestion persist despite diuretic administration, or if the prescribed fluid balance cannot be achieved, escalation of treatment (i.e. dose and/or frequency) is the first step, followed by diuretic combination therapy, together with minimization of fluid intake [2] (Fig. 1). Of note, it is also possible for intravascular hypovolaemia and renal congestion to be present at the same time, for instance in case of intraabdominal compartment syndrome. In this situation, haemodynamic resuscitation and correction of the underlying pathology are the priority.

What if serum creatinine rises?

Whilst diuretics are not nephrotoxic per se, excessive fluid depletion can lead to decreased renal perfusion and a fall in glomerular filtration. A slight increase in SCr is suggestive of hemoconcentration and effective fluid depletion ("pseudo-worsening of renal function"). Decongestion in heart failure is associated with improved clinical outcomes and often outweighs the risks associated with SCr changes. In contrast, persistent congestion in the face of worsening renal function is associated with worse outcomes. Therefore, decongestion should be prioritised. Where available, tubular damage biomarkers (e.g. cell cycle arrest markers, neutrophil gelatinase associated lipocalin, Kidney injury molecule-1) may be helpful in differentiating true kidney injury from the expected creatinine changes resulting from decongestion [5].

Which adverse effects are anticipated?

Loop diuretics may cause hypokalemia, hypernatremia, hypomagnesemia, hypophosphatemia, hypocalcemia, and metabolic alkalosis (Fig. 1). More serious side effects include uric acid retention and ototoxicity but the exact frequency in critically ill patients is not known. Thiazides can cause hyponatremia, and acetazolamide promotes metabolic acidosis.

Is continuous infusion more effective than intermittent dosing?

Continuous infusions offer advantages of consistent plasma concentrations, greater time in the therapeutic range and more reliable administration. Bolus administration of loop diuretics allows for an assessment of diuretic responsiveness and is often recommended prior to initiating a continuous infusion. Studies comparing both methods have demonstrated improved diuresis and fluid balance with continuous administration but no difference in mortality, length of hospital stay, and adverse outcomes [6–8].

Is there a role for combining diuretics with albumin to improve effectiveness?

Loop diuretics are organic anions highly bound to albumin (> 90%) and undergo proximal tubular secretion by organic anion transporters (OATs) before reaching their site of action [9]. Hypoalbuminemia results in a higher plasma free fraction and less delivery to the site of action [9]. A meta-analysis demonstrated improved diuresis when intravenous albumin was administered prior to loop diuretics, especially in patients with a serum albumin < 2.5 g/dL, impaired kidney function or when using higher albumin doses [10]. However, significant heterogeneity across these studies was noted. Albumin replacement should be reserved as a tool after escalation of doses and combination therapy has been employed (Fig. 1).

What is the role of the furosemide stress test

The furosemide stress test (FST) is a diagnostic tool to evaluate tubular function. Since furosemide effectiveness is completely dependent on tubular function, the diuretic response can be viewed as an indicator of tubular integrity in patients with AKI. Chawla et al. showed that an urine output of < 200 mL in 2 h following a single dose of furosemide (1 mg/kg for diuretic naïve patients and 1.5 mg/kg for patients who had received diuretics) had good predictive value for AKI progression [11]. Further, the FST was feasible, safe and well tolerated.

How to manage diuretic resistance

Diuretic resistance may be due to several factors including haemodynamic instability with poor drug delivery to the site of action, kidney disease, hypoalbuminemia, compromised tubular integrity and function, intravascular hypovolemia, and drug competition at OAT site (e.g. non-steroidal anti-inflammatory drugs, β-lactams, methotrexate, urate and urea) [12, 13]. Importantly, as GFR declines, proximal tubular secretion of loop diuretics is reduced, and less drug is available at the site of action.

Loop diuretic efficacy is limited by post-diuretic renal salt retention due to extracellular volume depletion and volume-independent sodium retention manifest as an inability to excrete a modest sodium chloride load [14]. Management consists of addressing the contributing factors and combination therapy with thiazides, MRA's or acetazolamide (Fig. 1). For patients with acute heart failure, there is also a role for combining sodium–glucose co-transporter-2 inhibitors with loop diuretics [15]. Extracorporeal methods including renal replacement therapy should be considered in case of continued fluid accumulation despite maximum diuretic therapy, or if escalation of diuretics is not safe due to major adverse effects [16].

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Declarations

Conflicts of interest

MO, LA and ML report no conflict of interest related to the content of the manuscript.

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